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Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation caffeine citrate for the treatment of primary apnoea of premature newborns

On 17 February 2003, orphan designation (EU/3/03/132) was granted by the European Commission to Combino Pharm, S.L., Spain, for caffeine citrate for the treatment of primary apnoea of premature newborns.

The sponsorship was transferred to Chiesi Farmaceutici S.P.A., Italy, in January 2007.

What is primary apnoea of premature newborns?

Babies that are born well before the due date are called "premature newborns". These babies can have problems with breathing. They can stop breathing for a short time. When this lasts 20 seconds or longer, it is called apnoea. Generally, it is not clear what causes babies to stop breathing. When the causes are not known then this is called primary apnoea. Probably, it is due to the fact that the babies are born early and the organs and tissues of these babies are not yet mature. This includes the parts of the brain and the muscles that control the breathing. When babies stop breathing then this can cause very serious damage to the brain.

What is the estimated number of patients affected by the condition?

At the time of designation, primary apnoeas of premature newborns affected between 0.5 and 1.2 in 10,000 people in the European Union (EU)*. This is equivalent to a total of 19,000 and 45,000 people, and is below the threshold for orphan designation, which is 5 people in 10,000. This is based on the information provided by the sponsor and the knowledge of the Committee for Orphan Medicinal Products (COMP).

What treatments are available?

Several medicines and other treatments are used to treat premature babies who do not breathe well. Satisfactory argumentation has been submitted by the sponsor to justify the assumption that the medicinal product subject of the application might be of potential significant benefit for the treatment

*Disclaimer: The number of patients affected by the condition is estimated and assessed for the purpose of the designation, for a European Community population of 377,000,000 (Eurostat 2001) and may differ from the true number of patients affected by the condition. This estimate is based on available information and calculations presented by the sponsor at the time of the application.



of primary apnoeas of premature newborns. The main reason is that caffeine citrate would be widely available in the European Union. This will have to be proven at the time of marketing authorisation. This will be necessary to maintain the orphan status.

How is this medicine expected to work?

Caffeine citrate stimulates the nervous system in the brain. In patients with primary apnoeas, caffeine can activate the part of the brain that controls breathing. Caffeine may also act in other ways. It may increase sensitivity to carbon dioxide that builds up in the body during apnoea. Patients might breathe more if a gas called carbon dioxide builds up in the body (as happens in apnoea). In addition it may improve respiratory muscle tonus and decrease diaphragm fatigue. The lungs could breathe in and out larger amount of air. The muscles used for breathing may contract more easily and may become less tired from breathing.

What is the stage of development of this medicine?

At the time of submission of the application for orphan designation, clinical trials in premature newborns with primary apnoea were completed. Caffeine citrate has already been granted marketing authorisation in the condition subject of the application in France.

Caffeine citrate is designated as orphan in the United States in the treatment of apnoea of prematurity (20 September 1998). The same product has been licensed in the United States in the orphan condition on 21 September 1999.

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 10 January 2002 recommending the granting of this designation.

Update: Caffeine citrate (Peyona, previously Nymusa) has been authorised in the EU since since 2 July 2009 for treatment of primary apnoea of premature newborns.

More information on Peyona can be found in the European public assessment report (EPAR) on the Agency's website: ema.europa.eu/Find_medicine/Human_medicines/European_Public_Assessment_Reports

Opinions on orphan medicinal product designations are based on the following three criteria:

- the seriousness of the condition;
- the existence of alternative methods of diagnosis, prevention or treatment;
- either the rarity of the condition (affecting not more than 5 in 10,000 people in the EU) or insufficient returns on investment.

Designated orphan medicinal products are products that are still under investigation and are considered for orphan designation on the basis of potential activity. An orphan designation is not a marketing authorisation. As a consequence, demonstration of quality, safety and efficacy is necessary before a product can be granted a marketing authorisation.

For more information

Sponsor's contact details:

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For contact details of patients' organisations whose activities are targeted at rare diseases see:

- [Orphanet](#), a database containing information on rare diseases which includes a directory of patients' organisations registered in Europe.
- [European Organisation for Rare Diseases \(EURORDIS\)](#), a non-governmental alliance of patient organisations and individuals active in the field of rare diseases.

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Translations of the active ingredient and indication in all official EU languages¹, Norwegian and Icelandic

Language	Active ingredient	Indication
English	Caffeine citrate	Treatment of primary apnoea of premature newborns
Bulgarian	Кофеин цитрат	Лечение на първична апнея при недоносени
Czech	Citrát kofeinu	Léčba primární apnoe u předčasně narozených novorozenců
Danish	Koffeincitrat	Behandling af primær apnø hos præmature nyfødte
Dutch	Cafeïne-citraat	Behandeling van primaire apnea bij prematuur pasgeborene
Estonian	Kofeiinsitraat	Enneaegsete vastsündinute primaarse apnoe ravi
Finnish	Kofeiinisitraatti	Keskosilla esiintyvän primaarisen apnean hoito
French	Citrate de caféine	Traitement de l'apnée idiopathique du prématuré
German	Koffeincitrat	Behandlung von primärer Apnoe bei Frühgeborenen
Greek	Κιτρική καφεΐνη	Θεραπεία πρωτοπαθούς άπνοιας πρόωρων νεογνών
Hungarian	Koffein citrát	Koraszülöttekben kialakult primer apnoea kezelése
Italian	Citrato di caffeina	Trattamento dell'apnea idiopatica nei neonati prematuri
Latvian	Kofeīna citrāts	Primāra elpas trūkuma ārstēšana priekšlaicīgi dzimušiem bērniem
Lithuanian	Kofeino citratas	Pirminės apnėjos gydymas neišnešiotiems naujagimiams
Polish	Kofeiny cytrynian	Leczenie pierwotnego bezdechu u wcześniaków
Portuguese	Citrato de cafeína	Tratamento de apneia primária do recém-nascido prematuro
Romanian	Citrat de cafeină	Tratamentul apneei primare la nou-născuții prematuri
Slovak	Citrát kofeinu	Liečba primárneho spánkového apnoe u predčasne narodených detí
Slovenian	Kofein citrat	Zdravljenje primarne apneje pri nedonošenčkih
Spanish	Citrato de cafeína	Tratamiento de la apnea primaria del neonato
Swedish	Koffeincitrat	Behandling av primär apné hos prematurt nyfödda barn

¹ At the time of transfer of sponsorship